AAOS Now

Warning: Local anesthetics may be toxic to articular cartilage

By Annie Hayashi

Amount, duration of local anesthetics can be cytotoxic

When **Constance R. Chu, MD,** began exploring the possibility that local anesthetics could have a toxic effect on articular chondrocytes, she was concerned by what she found. "The results from the first study we conducted were shocking," she said. "The local anesthetic agents were so toxic, I could not believe it. We observed greater than 99 percent bovine chondrocyte death after a 15-minute exposure to a 0.5 percent bupivacaine solution."

That finding spurred Dr. Chu and her team to conduct additional research. Her most recent study, "The in vitro effects of bupivacaine on articular chondrocytes," appears in the June 2008 *Journal of Bone and Joint Surgery* (British edition).

This study, she said, puts the issue in perspective. "Surgeons have used local anesthetics for decades in small quantities by single intra-articular injection without apparent negative clinical effects," Dr. Chu explained. But when surgeons started to administer local anesthetics by continuous infusion for postoperative pain control, some began to see unexplained cartilage loss in young patients after routine procedures.

"Our studies show that if too much local anesthetic is used or if it is used for too long, the toxicity to cartilage cells can be quite profound," she said. Low-dose injections administered on an infrequent basis, however, may not present a problem.

Putting bupivacaine to the test

Dr. Chu and her research team measured the effects of different doses of bupivacaine, administered for various periods, on articular cartilage and the osteochondral cores of bovine and human specimens.

In one experiment, 24 bovine osteochondral cores were divided into 8 equal groups. Four groups were left intact, and 1 mm of cartilage was removed from the cores in the remaining 4 groups.

Three intact bovine osteochondral cores and three cores with 1 mm of cartilage removed were then randomly placed into solutions of 0.9 percent saline (control), 0.5 percent bupivacaine, 0.25 percent bupivacaine, or 0.125 percent bupivacaine for 30 minutes.

Cores with intact surfaces showed increased surface and subsurface chondrocyte death only when exposed to the 0.5 percent bupivacaine solution. Cores with the top 1 mm of cartilage removed showed increased subsurface chondrocyte death in both 0.5 percent and 0.25 percent bupivacaine solutions (Table 1).

These results, showing cytotoxicity after prolonged exposure to low doses of bupivacaine, indicated that bovine cartilage without an intact articular surface was more vulnerable to bupivacaine. Dr. Chu then turned her attention to human articular cartilage, using tissue harvested from donors and knee replacement patients.

Because some dead cells were present in all human articular cartilage specimens, the investigators simplified the testing process and left the articular surfaces intact.

Five specimens were placed in a 0.5 percent bupivacaine solution and five in a 0.9 percent saline solution for 30 minutes. Each specimen was evaluated with confocal microscopy for live and dead cells by quantitative analysis of 3-dimensional reconstructions of the articular cartilage.

Specimens exposed to the 0.5 percent bupivacaine solution had a 1.7-fold increase in dead chondrocytes in their subsurface region compared to the controls.

Alginate-bead cultures become test medium

Dr. Chu and her research team also conducted 100 experiments using more than 3,000 alginate bead cultures. The articular cartilage for these tests was harvested as full-thickness slices, minced, and the chondrocytes extracted.

After the chondrocytes had been encapsulated in the alginate-bead culture for a week, the alginate beads were divided into experimental groups and immersed in

1 mL of bupivacaine hydrochloride (0.5 percent, 0.25 percent, and 0.125 percent solutions) for 15, 30, or 60 minutes.

The beads were then removed from the bupivacaine solutions, washed, and "incubated in chondrocyte growth media," according to Dr. Chu. The viability of the cells was assessed at 1 hour, at 24 hours, and at 1 week, using flow cytometry.

In 28 experiments—12 with bovine and 16 with human alginate bead cultures—the team also adapted time-lapse, cell-imaging methods so they could observe the viability of chondrocytes exposed to bupivacaine.

Effects of dose and time on chondrocyte viability

Analysis of data from 72 flow cytometry experiments showed a dose- and time-dependent chondrotoxicity to bupivacaine solutions.

For both human and bovine chondrocytes, more than 95 percent chondrocyte death and apoptosis occurred after exposure to 0.5 percent bupivacaine at all three exposure times, consistent with the results of the previous study.

Bovine chondrocytes exposed to 0.25 percent bupivacaine had decreased viability when compared to those exposed to the saline solution. The 0.125 percent dose proved to be more benign and its effects on bovine chondrocytes were similar to that of the normal saline solution.

The data from time-lapse confocal microscopy experiments also showed a dose-dependent chondrotoxicity after continuous exposure to 0.5 percent and 0.25 percent bupivacaine solutions, with human and bovine cartilage cells dying more rapidly during exposure to 0.5 percent bupivacaine. Chondrocyte viability after exposure to 0.125 percent bupivacaine was similar to saline for all experiments.

Effects of bupivacaine on articular cartilage

Confocal microscopy revealed that both bovine and human osteochondral cores showed chondrotoxicity following exposure to 0.5 percent bupivacaine. The intact articular surface proved to be partially protective.

When the top 1 mm of articular cartilage was removed, the bovine osteochondral tissues showed increased chondrocyte death when exposed to 0.25 percent bupivacaine.

Extensive flow cytometry experiments showed near complete human and bovine chondrocyte death following exposure to 0.5 percent bupivacaine and a progressive decline in chondrocyte viability with greater exposure times and with increased time after exposure to 0.25 percent bupivacaine.

What is the bottom line for clinicians?

"Although I think it is inappropriate to draw clinical conclusions from this type of study," explained Dr. Chu, "the data does provide important information for clinicians. It shows a dose- and time-dependent cytotoxicity following relatively brief exposure to 0.5 percent and 0.25 percent bupivacaine.

"To me," she continued, "this supports caution in prolonged exposure of articular cartilage to bupivacaine solutions. It also suggests that the potential for chondrotoxicity is higher with continuous intra-articular infusion of bupivacaine over long periods of time than with a one-time injection.

"Given that 0.125 percent bupivacaine had similar effects as saline, I believe the potential for clinically significant cartilage damage is quite low with the occasional single injection of a small amount of bupivacaine into a large joint. Recent clinical reports, however, do raise concerns about rapid loss of articular cartilage following continuous infusion of bupivacaine into relatively

confined joints such as the shoulder.

"In other studies, we have also shown that lidocaine has dose- and time-dependent toxic effects on chondrocytes so this may be a class effect of local anesthetics.

"As such, I have modified my own practice to eliminate bupivacaine use where possible, and to use the lowest concentrations of local anesthetics for the shortest period of time needed to achieve specific clinical effects," Dr. Chu concluded. "I also believe it would be prudent to avoid continuous intra-articular infusion of local anesthetics pending further in vivo study."

Disclosure information for Dr. Chu can be found at www.aaos.org/disclosure

Annie Hayashi is the senior science writer for AAOS Now*. She can be reached at hayashi@aaos.org*

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6300 North River Road Rosemont, Illinois 60018-4262 Phone 847.823.7186 Fax 847.823.8125